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Nonlymphoid Gastrointestinal Malignancies in Turkish Children

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Nonlymphoid gastrointestinal malignancies are not frequently encountered malignant tumors of childhood. From 1972 to 1994, at Hacettepe University Children's Hospital, there were 6,774 malignant tumors encountered in patients from birth to age 17. Thirty-five of them (0.5%) originated from the gastrointestinal tract. There were five carcinoid tumors, four pancreas tumors (two were solid-cystic tumors), four APUDomas, three leiomyosarcomas, one mesothelioma, two carcinomas of the stomach and duodenum, and 16 colon and rectum carcinomas (12 were mucin-producing). These rare tumors are discussed according to the characteristics of the patients, therapy modalities applied, and outcome of the patients.

Key words: childhood, pancreatic tumors, colorectal carcinoma, leiomyosarcoma, APUDoma

INTRODUCTION

Nonlymphoid gastrointestinal malignancies are not frequently encountered malignant tumors of childhood. From 1972 to 1994 at Hacettepe University Children's Hospital there were 6,774 malignant tumors encountered in patients from birth to age 17. Thirty-five of them (0.5%) originated from the gastrointestinal tract. There were five carcinoid tumors, four pancreas tumors, four APUDomas, three leiomyosarcomas, one mesothelioma, two carcinomas of the stomach and duodenum, and 16 colon and rectum carcinomas. This report is a retrospective review of the experience of Hacettepe University Pediatric Oncology Unit in a period of 22 years.

PATIENTS AND METHODS

Carcinoid Tumors

This group consists of five patients (M:F = 2/3) with an age range of 7 to 16 years (median 13 years) (Table I). The most common presenting symptom was abdominal pain. Four of the carcinoid tumors were located in the appendix and after appendectomy no therapy was given. Urinary 5-hydroxyindoleacetic acid (5-HIAA) levels were normal in these patients. Only one patient with malignant carcinoid tumor died of recurrent disease in a period of 15 months despite chemotherapy, radiotherapy, and surgery.

APUDomas

This group consists of four patients (M:F = 3/1) ages ranging from 6 to 14 years (median 13 years) (Table II). Their main complaint was abdominal mass and distention. Gastroenteropancreatic hormone levels could not be measured because of the restricted laboratory facilities of the hospital in the past years. Except for third patient, all the others had large abdominal masses which could not be resected. Three of the patients received chemotherapy. Two of them are alive, and one has three healthy children. The third one is lost to follow-up. The fourth patient did not accept the therapy.

Pancreatic Tumors

Four patients (M:F = 2/2) ages ranging from 6 to 12 years (median 10 years) were diagnosed (Table III). Their main complaint was abdominal pain and distention. Also, jaundice and weight loss were noted. Three of the tumors originated from the pancreas. Origin of the epigastric mass in the third patient was difficult to determine because of disseminated disease. Histopathologic examination revealed two solid-cystic tumors, one acinar cell carcinoma, and one malignant epidermoid tumor which

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TABLE I. Characteristics of Patients With Carcinoid Tumors

Patient	Age (yr)	Sex	Date of admission	Complaint	Primary site	Histology	Metastases at diagnosis	Operation	Serologic markers	Chemotherapy and RT*	Survival
1	7	M	1974	Fever, abdominal pain	Ileum	Malignant carcinoid	Bladder invasion, multiple, mesenteric nodes	1st operation: ilococecal resection	Not studied	—	
							Rectosigmoid infiltration	2nd operation sigmoid colostomy	5-FU[a] and RT[b]	5-FU[a] and RT[b]	Died of progressive disease in 15 months
2	16	F	1983	Nausea, abdominal pain	Appendix	Carcinoid	—	Appendectomy	Urinary 5-HIAA negative	—	No follow-up
3	13	F	1987	Nausea, abdominal pain	Appendix	Carcinoid	—	Appendectomy	Urinary 5-HIAA negative	—	Alive
4	13	M	1988	Fever, abdominal pain	Appendix	Carcinoid	—	Appendectomy	Urinary 5-HIAA negative	—	Alive
5	15	F	1993	Abdominal pain	Appendix	Carcinoid	—	Appendectomy	Urinary 5-HIAA negative	—	Alive

[a]5-FU: 5-fluorouracil.
[b]RT: radiotherapy.

could not be further subgrouped. Metastases at diagnosis, therapy modalities, and data about survival of the patients are listed in Table III. Two of the patients were lost to follow-up and the other two with solid-cystic tumors are alive for 1.5 and 3 years, respectively.

Leiomyosarcomas

Three patients, (M:F = 2/1) ages ranging from 3 to 15 years (median 9 years) were diagnosed (Table IV). Their main complaints were abdominal pain, distention, and weight loss. One of the tumors originated from the stomach, the other two from terminal ileum and jejenum, respectively. Because of the invasion of colon, spleen, and pancreas, the gastric leiomyosarcoma was treated with chemotherapy and radiotherapy. The patient died of progressive disease in a period of 2 months from the diagnosis. The first patient with ileal tumor died of progressive disease in a period of 16 months, although ileum resection was performed and chemotherapy and radiotherapy was administered. The third patient is diagnosed recently with disease in the terminal ileum and jejenum. Resection has been performed. Paraaortic lymph nodes are disease-positive and chemotherapy is planned.

Mesothelioma

Malignant peritoneal mesothelioma was diagnosed in a 15-year-old boy who complained of abdominal pain and distention (Table V). Laparotomy was performed and a tumor of 10 cm in diameter was found arising from the omentum. Excision of the tumor and omentectomy was carried out. Chemotherapy was started but the patient was lost to follow-up.

Gastric and Duodenal Cancer

Adenocarcinoma of the stomach arising from the lesser curvature was diagnosed in a 14-year-old boy who had abdominal pain, distention, nausea, vomiting, and weight loss (Table V). Gastroscopic biopsy and laparotomy were performed and, because of abdominal dissemination, only biopsy was performed. The patient did not accept any kind of treatment.

Anaplastic carcinoma arising from the duodenum was diagnosed in a 12-year-old male who complained of abdominal distention. Laparotomy and biopsy were performed because of disseminated disease in the abdomen. This patient also did not accept any kind of therapy and was lost to follow-up.

Carcinoma of the Colon and Rectum

In this group there were 16 subjects whose age at diagnosis ranged from 11 to 16 years (median 13 years) and M:F ratio was 9/7 (Table VI). There was no history of ulcerative colitis or familial polyposis or another precancerous lesion in any of the patients. Localization of the disease is seen in Figure 1. The most common presenting

TABLE II. Characteristics of Patients With APUDomas*

Patient	Age (yr)	Sex	Date of admission	Complaint	Primary site	Histology	Metastases at diagnosis	Operation	Chemotherapy	Survival
1	14	F	1979	Abdominal mass, distention	20 × 17 × 17 cm mass infiltrating left kidney, spleen, pancreas	APUDoma	Disseminated disease to the left kidney, spleen, pancreas	Splenectomy + left nephrectomy + pancreatic tail resection + left subtotal surrenal resection	CDDP, MTX, CYC, 5-FU, VCR	Afer 1.5 years of chemotherapy, still alive without disease.
2	14	M	1985	Abdominal distention	20 × 20 cm mass at the root of the mesentery	APUDoma	Disseminated disease to bilateral kidneys, aorta, and inferior vena cava	Laparotomy + biopsy	Doxorubicin × 4 cycle M-CCNU, 5-FU × 12 cycle, radiotherapy, CDDP, VCR, CYC, MTX, 5-FU 1 year	After 3 years of therapy patient is alive with stable mass for 6 years.
3	12	M	1986	Abdominal mass	Pancreas corpus (34 × 24 mm)	APUDoma		80% resection of the pancreatic tumor	CDDP, MTX, CYC, 5-FU, VCR	After 9 months of chemotherapy mass in the pancreas disappeared. Then lost to follow-up.
4	6	M	1987	Abdominal distention, mass, and vomiting	20 × 20 cm mass infiltrating transverse colon, ascending colon, and large intestine	APUDoma	Disseminated disease to the small and large intestine	Laparotomy, biopsy		Family did not accept further therapy. Lost to follow-up.

*CDDP: Cis-platinum, MTX: methotrexate, CYC: cyclophosphamide, 5-FU: 5-fluorouracil, VCR: vincristine.

TABLE III. Characteristics of Patients With Pancreatic Tumors*

Patient	Age (yr)	Sex	Date of admission	Complaint	Primary site	Histology	Metastases	Operation	Chemotherapy	Survival
1	10	M	1976	Abdominal trauma, abdominal distention	Pancreas head	1st operation: pancreatic cyst 2nd operation: pancreatic tumor 3rd operation: malignant epitheloid tumor		Gastrojejunostomy		Seven months after the 1st and 2nd operation was performed and 10 × 12 × 15 cm mass infiltrating the 2nd part of duodenum was excised and gastrojejunostomy performed. After 10 months without therapy recurrent mass of 15 × 15 cm stomach localization and metastasizing to liver were observed. CCNU, 5-FU began and changed to CYC, VP-16, procarbazine, prednisolone. During the 11-month period, disease was progressive and patient was lost to follow-up.
2	6	F	1977	Abdominal distention, pain, weight loss	Pancreas	Acinar cell carcinoma	Liver, diffuse abdominal dissemination	Laparotomy + biopsy		Lost to follow-up
3	10	M	1991	Abdominal pain	Epigastric 18 × 10 cm mass	1st operation: neuroblastoma	Lung, liver	Laparotomy + biospy	VCR, CYC, CDDP × 3 cycle, radiotherapy, VCR, CYC, DTIC, doxorubicin × 9 cycle	Liver metastasis disappeared and mass was 1/2 regressed. Second-look operation was performed.
						2nd operation: solid cystic tumor of pancreas	Stable lung metastasis	Resection of the residual disease		The patient was followed without any therapy after the 2nd operation when the diagnosis was changed. After a period of 1 year, recurrent disease at the pancreatic region was detected. Patient has been receiving chemotherapy since Oct. 1993.
4	12	F	1993	Abdominal distention, jaundice, failure to thrive	Pancreas head	Solid cystic tumor of pancreas		Resection of the tumor mass at the head of pancreas		Alive for 1.5 years

*VCR: Vincristine, CYC: cyclophosphamide, CDDP: CIS-platinum.

TABLE IV. Characteristics of Patients With GIS Leiomyosarcomas*

Patient	Age (yr)	Sex	Date of admission	Complaint	Primary site	Histology	Metastases at diagnosis	Operation	Chemotherapy	Survival
1	9	M	1975	Abdominal pain, diarrhea, vomiting	15 × 10 × 10 cm mass originating from ileum	Leiomyosarcoma	Pelvic, peritoneal implants	30 cm ileum resection	VCR, ACT-D, CYC, doxorubicin	After a period of 10 months, recurrent abdominal disease, liver metastasis was observed. Radiotherapy administered. Chemotherapy was switched to CDDP but the patient died of disease in a period of 1 year from the diagnosis.
2	3	F	1981	Abdominal pain, weight loss	Greater curvature of the stomach	Leiomyosarcoma	Colon, spleen, pancreas	Laparotomy + biopsy	VCR, CYC, doxorubicin + radiotherapy	Died with progressive disease in a period of 2 months.
3	15	M	1994	Abdominal pain, nausea, vomiting, and weight loss	Terminal ileum	Malignant leiomyoblastoma (epitheloid leiomyosarcoma)		Terminal ileum and 30 cm jejenum resection	VCR, CYC, EPR, ACT-D initiated	

*VCR: vincristine, ACT-D: actinomycin D, CYC: cyclophosphamide, EPR: epirubicine.

TABLE V. Characteristics of Patients With Gastric and Duodenal Carcinomas and Mesothelioma*

Patient	Age (yr)	Sex	Date of admission	Complaint	Primary site	Histology	Metastases at diagnosis	Operation	Chemotherapy	Survival
1	14	M	1975	Abdominal distention, nausea, vomiting, abdominal pain	Lesser curvature of the stomach	Adenocarcinoma	Diffuse abdominal dissemination	Laparotomy, biopsy	—	Lost to follow-up
2	12	M	1977	Abdominal distention	Duodenum	Anaplastic carcinoma	Ascites, diffuse abdominal dissemination	Laparotomy, biopsy	—	Lost to follow-up
3	15	M	1988	Abdominal pain	Omentum majus	Mesothelioma	—	Omentectomy	VCR, ACT-D, CYC, doxorubicin	Lost to follow-up

*VCR: vincristine, ACT-D: actinomycin D, CYC: cyclophosphamide.

TABLE VI. Characteristics of Patients With Colorectal Carcinoma

Patient	Age (yr)	Sex	Primary site	Histology[a]	Stage at diagnosis	Documented metastases at diagnosis	Operation	Survival
1	13	M	Rectum	Mucoid	D	Mesenteric nodes, peritoneum	Abdominoperineal resection	Died in 6 months
2	14	F	Rectum	Non-mucoid	D	Liver	Refused operation	Died in 1 month
3	13	F	Rectosigmoid	Non-mucoid	C	Iliac nodes (+)	Abdominoperineal resection	Died in 6 months
4	11	M	Transverse colon	Non-mucoid	D	Intra-abdominal diffuse metastases, liver, abdominal wall, peritoneum	Exploratory laparotomy, biopsy	Died first post-operative day
5	14	F	Rectum	Mucoid	D	Peritoneum	Exploratory laparotomy, transverse loop colostomy	No follow-up
6	13	M	Rectum	Non-mucoid	D	Peritoneum	Abdominoperineal resection	Died in 9 months
7	12	M	Sigmoid	Mucoid	D	Omentum, peritoneum	Exploratory laparotomy, biopsy	No follow-up
8	13	M	Cecum	Mucoid	C	Mesenteric nodes	Ileocecal resection, ileocolic anastomoses	Followed 4 years, no later follow-up
9	16	M	Hepatic flexure	Mucoid	C	Mesenteric nodes	Ileocecal resection, ileocolic anastomoses	Died in 1 year
10	15	F	Descending colon	Mucoid	D	Mesenteric nodes, peritoneum, omentum	Transverse loop colostomy	Died in 6 months
11	11	F	Rectosigmoid	Mucoid	D	Mesenteric nodes, peritoneum	Rectosigmoid resection, colostomy	Died in 8 months
12	16	M	Sigmoid	Mucoid	D	Omentum, peritoneal carcinomatosis	Exploratory laparotomy, biopsy	No follow-up
13	14	F	Rectum	Mucoid	D	Peritoneal carcinomatosis	Colostomy	No follow-up
14	13	M	Sigmoid	Mucoid	C	Mesenteric nodes	Sigmoid colon resection, colostomy	No follow-up
15	14	M	Hepatic flexure	Mucoid	D	Omentum	Ileocecal resection	Died in 12 days
16	13	F	Transverse colon	Mucoid	D	Omentum, mesenteric nodes	Exploratory laparotomy, biopsy	Died in 1 month

[a]All histopathologic diagnoses were adenocarcinomas.

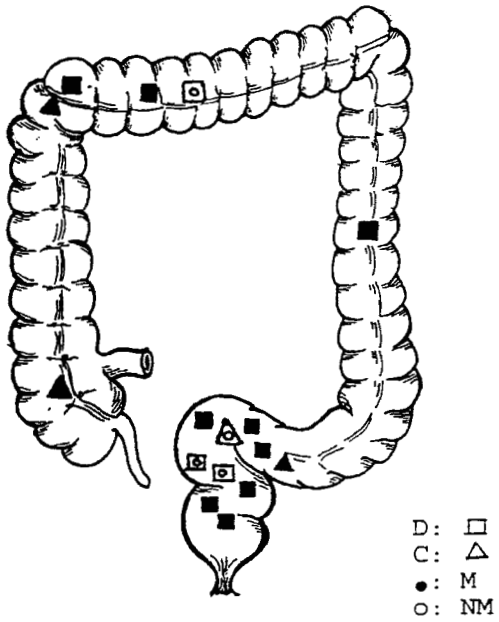

Fig. 1. Distribution, histologic features, and stages of colon cancer. D: Dukes' stage D; C: Dukes' stage C; M: mucinous type of adenocarcinoma; NM: nonmucinous histologic findings.

symptom was abdominal pain, followed by rectal bleeding, abdominal distention, weight loss, nausea, vomiting, anorexia, and intestinal obstruction, respectively. Four patients had nonmucinous adenocarcinoma. The remaining patients had mucin-producing tumors. Four patients had Dukes' Stage C disease and 12 had Stage D disease. Types of the operations performed are seen in Table VI. Most of the patients had significant residual tumor after the initial surgical procedure. Chemotherapy used to treat six of these patients consisted of 5-fluorouracil (5-FU). Six subjects received 5-FU, CCNU, and another group of three subjects received 5-FU, doxorubicin, and mitomycin. None of the patients could be followed up to determine the long time survival and the effects of chemotherapy. The only long term survivor (patient 8) had a primary cecum tumor, followed for 4 years.

DISCUSSION

Carcinoid tumors are uncommon in the pediatric age group. The largest series in the literature consists of only 30 cases [1,2]. They are epithelial tumors that may be benign or malignant and may be located in the esophagus or bronchi, or in the small or large bowel, pancreas, or ovary [3]. The most common site is the appendix, where most tumors are benign. Prognosis is relatively good even in the metastatic cases [4,5]. In our patients, 4 out of 5 were benign and located in the appendix. After performance of appendectomy no problem was observed during the long term follow-up. In the malignant case, the tumor was located in the ileum and resection was performed. Because of recurrent disease, the patient was operated on a second time following 3 months of chemotherapy and radiotherapy. He died of progressive disease in a period of 15 months. Clinical symptoms of carcinoid syndrome could be detected in none of the patients. Urinary levels of 5-HIAA were in normal ranges.

APUDomas are rare tumors that arise from endocrine cells of gastroenteropancreatic origin and secrete peptide hormones [6]. Most of them are found in the pancreas, but a few occur in the wall of the gut or in the retroperitoneum. Approximately 50% are malignant [6]. In our cases, two of them originated from the pancreas and the other two in the wall of the gut. Most of the patients had disseminated disease. Two of them underwent extended resection and only biopsy could be performed in the others. Most of the patients were treated by chemotherapy and radiotherapy. Half of the patients are alive, with or without disease, while the others are lost to follow-up. Any clinical manifestation of hormone secretion or concurrent endocrine tumors were detected in none of the patients.

Pediatric pancreatic cancers are a rare heterogenous group of malignancies with their prognosis dependent upon adequate resection and pathologic classification [3,7]. In our 22-year audit, we encountered four pancreatic tumors. One was acinar cell carcinoma, one was malignant epitheloid tumor without any further histologic discrimination, and the other two were solid-cystic tumors. In the literature, females outnumber males (1.2: 1.0) and the mean age at diagnosis is 7.9 ± 4.6 (SD) years [3,7]. Our patients' ages ranged from 6 to 12 years (mean 10 years) and M:F ratio was 2:2. Two of the patients had distant metastases at the time of diagnosis. Patients who underwent adequate resection had better prognosis compared to others.

Leiomyosarcoma is rare in childhood, accounting for less than 2% of soft tissue sarcomas in children [8]. They have recently been observed with increasing frequency in children with acquired immune deficiency syndrome [8]. In our series except the last patient who was diagnosed recently, the others died of progressive disease. HIV (human immunodeficiency virus) test is negative in this patient.

Malignant peritoneal mesothelioma is an uncommon tumor in all age groups and extremely rare in children [3,9]. The tumor arises from the surface of the mesothelial layer that covers pleural and peritoneal cavities and may also arise in some cases from the pericardium or the tunica vaginalis testis. In children, no correlation with aspestosis has been found [1]. The symptomatology is nonspecific so ambiguity of the symptomatology and the virulent malignancy of the tumor are responsible for the high mortality of the patients in the first year following

surgery. In our case, the patient had disseminated disease and chemotherapy was ineffective.

Gastric cancer is the exceptionally rare cancer of children and adolescents [3]. In our patient, tumor was localized at the lesser curvature of the stomach and disease was disseminated in the abdomen. The other patient had disease originating from the duodenum. He also had disseminated disease. Both of the patients were lost to follow-up.

A continuing problem affecting prognosis in children with colorectal carcinoma is the delay in early diagnosis. The initial and most common symptoms of vague abdominal pain coupled with constipation and diarrhea are not indicative of malignancy. Anemias are treated routinely without arousing the physician's suspicion. Adolescents generally do not wish to relate rectal bleeding with cancer, and are unlikely to volunteer this information. In our patients, the most common symptoms were abdominal pain and rectal bleeding. The predominant histologic pattern was mucin-producing adenocarcinoma in 12 of 16 patients. This subtype has been reported for most of the tumors of children and adolescents [3,10–13]. There is a notable preponderance of males among young patients [14–16]. Nine of sixteen patients in this series are boys. Regarding the primary tumor site there is no preponderance of any localization in young subjects. In our patients the most common primary site was the rectum [31%]. The survival of our patients was influenced by the very advanced stage of disease at presentation. Prolonged duration of symptoms and delay in diagnosis and poor responsiveness to nonsurgical modalities of treatment may have contributed significantly to the possible poor outcome for these patients. Median survival time was 6 months in the patients which we could follow. This survival pattern is similar to the reported series in the literature [14,17]. Surgery is the only modality known to be effective in providing cures. Adjuvant chemotherapy extends the life of individuals during childhood. Few patients who present with extensive metastatic disease are cured with chemotherapy [18]. Radiation has little to offer this tumor except when the tumor involves the rectosigmoid or anal canals.

In conclusion, although rare, nonlymphoid gastrointestinal malignancies should not be excluded from a clinical diagnosis in childhood on the basis of age only. Symptoms in children with abdominal pain are generally associated with mesenteric lymphadenitis, gastroenteritis, and appendicitis, whereas in adult patients cancer of the gastrointestinal system would be considered. It is suggested that barium enema x-rays and abdominal ultrasonographies be performed more frequently in children who have abdominal pain or vague abdominal symptoms presenting for more than 3 weeks.

Delay in early diagnosis, low follow-up rates, and refusal of the therapy protocols in advanced stages by the families are the major problems in the developing countries. Poor economic and cultural status of the parents are the most important factors. Those who practice pediatric oncology in this country believe that they will overcome these problems in the near future.

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